

REMARKS

This application pertains to a novel abuse-proofed dosage form. Claims 1, 2, 4, 7, 8, 27- 29, 31, 41 and 42 are pending.

Claims 1, 2, 4, 7, 8, 27-29, 31, 41 and 42 stand rejected under 35 U.S.C. 103(a) as obvious over Oshlack et al (US 2003/0064099/A1) in view of Zhang et al. (*Pharm. Dev. Tech.* **1999**, 4, 241-250) and further in view of Kumar et al (US 6,238,697B1) and DeJong (*Pharmaceutisch Weekblad Scientific Edition* **1987**, p24-28).

The Examiner views Oshlack as disclosing the preparation of dosage forms by *melt extrusion*, wherein a homogeneous mixture is heated to a temperature sufficient to at least soften the mixture, extruded through a twin-screw extruder which consists of two counter-rotating intermeshing screws, and then forcing the homogeneous mixture through a die to form strands. The Examiner sees this forcing process as providing some compaction.

The Examiner contends that the melt-extrusion technique of Oshlack et al. encompasses the heating technique of Applicants' claims.

Zhang is seen by the Examiner as disclosing the preparation of stabilized sustained release tablets by *hot-melt extrusion*.

Kumar is viewed by the Examiner as disclosing an extended release dosage form which comprises a high molecular weight polyethylene oxide binder.

Finally, the Examiner turns to DeJong for a calculation for determining crushing strength.

From all this, the Examiner concludes that it would have been obvious to use the PEO of high molecular weight of Zhang for the sustained release dosage forms of Oshlack, such as the PEO of Zhang which are used for the preparation of melt-extruded tablets via a melt-extrusion technique which, according to the Examiner

"...encompasses the sintering technique of the instant claims which recite press-forming with preceding exposure to heat."

Applicants' claims specifically recite that Applicants' dosage form is a sintered mass, and neither Oshlack nor any of the other references cited by the Examiner teaches or suggests anything about preparing a dosage form as a sintered mass.

Hawley's Condensed Chemical Dictionary, Thirteenth Edition, defines "sintering" as:

The agglomeration of metal or earthy powders at temperatures below the melting point. Occurs in both powder metallurgy and ceramic firing. While heat and pressure are essential, decrease in surface area is the critical factor. Sintering increases strength, conductivity and density.

From this, it is clear that sintering does not occur in a melted composition, and therefore cannot occur during melt extrusion.

Therefore, those skilled in the art reading Oshlack and the other references cited by the Examiner would understand that sintering could not possibly take place in Oshlack's melt extrusion process. Accordingly the Examiner's conclusion that Zhang's melt-extrusion technique "encompasses the sintering technique of the instant claims which recite press-forming with preceding exposure to heat" is technically not possible! The Examiner has not shown anything that would even remotely suggest that anything that could be learned from any of the references cited could ever lead to a sintered dosage form.

Those skilled in the art would recognize that sintering can not take place in Oshlack's twin screw extruder, with counter-rotating intermeshing screws, and nothing in Oshlack would even suggest that sintering would be possible in such equipment. Agglomeration would not occur in a twin extruder, with counter-rotating intermeshing screws.

The Examiner has not pointed to anything that would suggest to those skilled in the art that sintering could possibly take place in Oshlack's twin screw extruder.

Those skilled in the art would not expect sintering to take place in Zhang's melt-extrusion technique either, and the Examiner has not shown anything that would suggest that sintering could or would take place in Zhang's melt-extruder.

Accordingly, no person skilled in the art would ever believe that any combination of Oshlack, Zhang, Kumar and DeJong could ever lead to Applicants' novel sintered mass dosage form.

This rejection should be withdrawn for these reasons alone.

In addition, and as discussed in Applicants' last response, Oshlack relates to fundamentally different technology. The Oshlack reference pertains to a controlled release dosage form which includes, as the primary defense against abuse, aversive agents, such as a bittering agent or a viscosity increasing agent, which make abuse unpleasant, but do not in any way render the dosage form abuse-proofed. Oshlack contemplates that his dosage forms may be crushed or chewed. See paragraphs [0067 - 0068], where it is disclosed that Oshlack's aversive agents are "released" when the dosage form is e.g. chewed. Thus, Oshlack **discourages**, but does not necessarily prevent abuse. Oshlack's dosage forms **must** be tampered with in order to perform their intended function, i.e., to release the aversive agents. If somehow Oshlack's dosage forms were rendered crush-proof, as Applicants' dosage forms are, then Oshlack's point of novelty would be destroyed, and his dosage forms could not perform their intended function.

All of Oshlack's embodiments require that his dosage forms be capable of being chewed or crushed.

There is absolutely nothing in Oshlack pertaining to any dosage forms that could not be crushed or chewed. Any dosage form that could not be crushed or chewed would render Oshlack's invention inoperable. Should the Examiner disagree, she is respectfully asked to point out where in Oshlack she sees any dosage form that cannot be crushed or chewed.

Applicants achieve their high breaking strength by press-forming their dosage form with the simultaneous or preceding application of heat (paragraphs [0067] and [0117]). The dosage composition being compressed is heated to at least the softening temperature of component (C) [0067].

Oshlack does not disclose any such treatment for any dosage forms that remotely approach the composition of Applicants.

Oshlack, at paragraph [0111], indicates that his dosage form may be produced by melt-extrusion and/or pressed into tablets.

However, the composition that is melt extruded in paragraph [0111] does not comprise Applicants' polyalkylene oxide (C).

Nowhere is there any disclosure or suggestion of any compositions having a breaking strength of at least 500N, or of any technique whereby such a breaking strength might be obtained, or even the desirability of such a breaking strength. To the contrary, Oshlack is specifically directed to dosage forms that are susceptible to "tampering" and which release the aversive agents upon such tampering. Accordingly, Oshlack teaches away from Applicants' novel abuse-proofed dosage forms.

Applicants' claims require that the breaking strength of Applicants' dosage form be at least 500 N.

The Oshlack reference clearly teaches away from such a breaking strength in that it is an essential character of Oshlack's oral dosage form that it be chewable...see Oshlack's paragraph [0055]. Such chewing is essential in order for Oshlack's aversive agent to be released. If Oshlack's dosage form could not be chewed, the aversive agent would not be released and Oshlack's mechanism for discouraging tampering with the dosage form would not be realized.

If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. MPEP 2143.01. The principle of operation in Oshlack is that abuse will be reduced because an aversive agent is released from the dosage form when it is tampered with, e.g., crushed, ground

or chewed. A dosage form modified to meet the at least 500N breaking strength limitation of the instant claims cannot be tampered with in this manner and, therefore, Oshlack's principle of operation would be defeated. See specification, para. 8-9.

In re Ratti is instructive. In that case, the primary reference taught a device that required rigidity for operation, whereas the claimed invention required resiliency. The court reversed the rejection, holding that the "suggested combination of references would require ... a change in the basic principle under which the [primary reference] construction was designed to operate." See, *In re Ratti*, 270 F.2d 810, 813, 123 USPQ 349, 352 (CCPA 1959). Here, the prior art requires tampering by chewing, crushing or grinding for its operation, whereas the claimed invention requires a breaking strength which precludes such tampering. Modifying Oshlack in the manner the Examiner proposes would thus, as was the case in *Ratti*, change the basic principle under which the Oshlack construction was designed to operate.

As can be seen from the previously submitted publication Proeschel, *J Dent. Res* 81 (7):464-468, 2002, the mean human chewing force is about 200 N, which means that the breaking strength of Oshlack's dosage form must be no more than about 200 N; otherwise it could not be chewed and the aversive agent could not be released.

As previously discussed, the only disclosure of polyalkylene oxide in Oshlack is exclusively concerned with osmotic dosage forms (*Oshlack et al.*, [0148]-[0159]), which, however, are not sintered.

In another context, *Oshlack et al.* mentions methods for the preparation of matrix formulations which methods may be regarded as thermoforming, such as melt-extrusion (*Oshlack et al.*, [0111]). These matrix materials according to *Oshlack et al.*, however, do not encompass polyalkylene oxides (*Oshlack et al.*, [0097]).

Furthermore, in the dosage form according to claim 1 of the present application, the active ingredient is present in a controlled-release matrix of component (C). The active ingredient is embedded in the high molecular weight polyalkylene oxide that in turn serves as a retardant agent (specification, page 35, lines 13-19).

In contrast thereto, the release profile of the osmotic dosage forms according to *Oshlack et al.* does not rely on a controlled-release matrix, but on the expansion of the waterswellable high molecular weight polyalkylene oxides in the push layer, which does not contain the drug.

In other words, in the dosage forms according to the subject invention the high molecular weight polyalkylene oxide serves as a controlled-release matrix thereby retarding the release profile of the drug. In contrast thereto, in the osmotic dosage forms according to *Oshlack et al.*, a semi-permeable membrane hinders the drug from being released and the swelling of the high molecular weight polyalkylene oxide rather

causes the drug to leave the dosage form by pushing it through an orifice in the semipermeable membrane.

Therefore, the effect of the high molecular weight polyalkylene oxide in the matrix dosage forms of the present invention and in the osmotic dosage forms of the Oshlack reference are directly opposite to each other.

Further, Applicants' claims are limited to the use of polyethylene oxide having a molecular weight of 1-15 million, according to rheological measurements. Oshlack mentions the use of polyethylene oxide as a gelling agent, but does not teach or suggest anything about the use of polyethylene oxide having a molecular weight of 1-15 million. As can be seen from the previously submitted product description sheets the chemical supplier SIGMA-ALDRICH® commercializes polyethylene oxides having molecular weights of 10,000 g/mol and 100,000 g/mol, respectively, i.e. molecular weights which are 10 times and 100 times lower than the lower limit according to instant claim 1. Accordingly, Oshlack's disclosure of the use of polyethylene oxide as a gelling agent does not teach or suggest anything about the inclusion of polyethylene oxide in the 1-15 million molecular weight range as a hardening agent.

Further yet, Applicants' dosage forms require that the polyalkylene oxide be present in an amount sufficient to result in a breaking strength of at least 500 N. As shown by the previously submitted Rule 132 declaration, lesser amounts of polyethylene oxide did not achieve Applicants' breaking strength.

There is nothing in the reference that would teach or suggest anything about even the possibility of achieving such a breaking strength under any circumstances, let alone any hint that this could be achieved by including a sufficient amount of polyalkylene oxide and sintering.

Oshlack et al. is not a broad general disclosure containing a vast number of features that a skilled person would readily combine with one another, but a disclosure of distinct dosage forms having distinct properties based on distinct excipients and distinct processes of manufacture.

Oshlack et al. contains various sections dealing with different concepts of pharmaceutical technology by which to realize different dosage forms, each section containing a separate heading, e.g.:

- coated beads [0084]
- matrix formulation [0096]
- osmotic dosage forms [0148]
- transdermal delivery systems [0160]
- suppositories [0168].

A skilled person is fully aware that each section deals with another type of dosage form and nothing about any one of them would be thought to apply to any of the others. A skilled person would not follow the Examiner's approach to arbitrarily pick

individual features that are only disclosed in connection with a particular type of dosage form and combining them with other features disclosed in connection with other particular types of dosage forms.

In this regard, the Examiner's attention is respectfully drawn to MPEP 2141.02 (I), which provides that:

In determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious.

And MPEP 2141.02 (VI), which provides that:

A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. (citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984))

Accordingly, one of ordinary skill in the art, reading the reference as a whole, would not have picked one component from the section of the prior art dealing with one type of dosage form and combined it with a component from another section dealing with a different type of dosage form (at least not with predictable results or a reasonable expectation of success).

The Examiner has not pointed to anything that would lead to Applicants' invention as a whole!

The dosage forms according to the present invention can be regarded as matrix formulations where the polyalkylene oxide having a molecular weight of 1-15 million g/mol forms a matrix in which the active ingredient is embedded.

The entire section dealing with matrix formulations according to *Oshlack et al.* is completely silent on polyalkylene oxide having a molecular weight of 1-15 million g/mol.

The only disclosure of *Oshlack et al.* concerning polyethylene oxide having a molecular weight within the range of instant claim 1 of the present application is in connection with delivery or push layers of osmotic dosage forms (*Oshlack et al.*, [0150]-[0151]).

Said delivery or push layers of osmotic dosage forms, however, do not contain the drug. Instead, in osmotic dosage forms the drug is contained in a drug layer that is separate from said delivery or push layer.

The Examiner relies on the Zhang et al. reference for stabilized sustained release tablets prepared by hot melt extrusion, comprising PEO polymers of a molecular weight 1,000,000 and 7,000,000 in the matrix tablet prepared by hot-melt extrusion. As previously pointed out, Zhang uses the PEO as a drug carrier. This is completely different than Oshlack's use of polyethylene oxide as a hydrogel, as described in paragraph [0150] or as a "push layer" as described in paragraph [0151]. Nothing in either of these references would teach or suggest that Oshlack's dosage form should be

modified to include 74-88% PEO of a molecular weight 1,000,000 and 7,000,000. The maximum molecular weight of the PEO used by Oshlack as a hydrogel is 750,000 (see paragraph [0150]).

The Examiner's conclusion that it would have been obvious to use the PEO of high molecular weight of Zhang et al. for the sustained release dosage form of Oshlack is simply contrary to the teachings of these two references.

The Examiner relies on Kumar for a teaching that tablets having high molecular weight PEO binders from about 10 to about 20 percent by weight provide for a hard chip-resistant tablet, and DeJong for a relationship between specific crushing strength, porosity, friability and disintegration time described in mathematical terms.

Nothing in either Kumar or DeJong could possibly compensate for the deficiencies of Oshlack and Zhang with respect to the absence of anything that would teach or suggest the preparation of a sintered mass dosage form, or any other dosage form configuration that would have a breaking strength of at least 500N.

Contrary to the Examiner's assertions, nothing in Kumar teaches or suggests any tablet having a crushing strength of at least 500N. Kumar's chip-resistance has nothing to do with crushing strength.

The Examiner's attention is respectfully drawn to the definition of breaking strength found in Applicants' specification, beginning at page 37, line 24. Those skilled in the art will understand from Applicants' description of the method for determining breaking strength that chip resistance is unrelated to breaking strength. In fact, at page 38, lines 16-19, Applicants teach that:

The tablets deemed to be resistant to breaking under a specific load include not only those which have not broken but also those which may have suffered plastic deformation under the action of the force.

Clearly, chip resistance is not an indicia of breaking strength.

Further, nothing about DeJong's calculation technique would overcome the basic deficiencies of the Oshlack/Zhang combination of references.

From the foregoing it is clear that the Examiner has not shown that Applicants' novel abuse-proofed dosage form as a whole is obvious over the references cited.

The rejection of claims 1, 2, 4, 7, 8, 27-29, 31, 41 and 42 under 35 U.S.C. 103(a) as obvious over Oshlack et al. (US 2003/0064099/A1) in view of Zhang et al. (*Pharm. Dev. Tech.* **1999**, 4, 241-250) and further in view of Kumar et al (US 6,238,697B1) and DeJong (*Pharmaceutisch Weekblad Scientific Edition* **1987**, p24-28) should therefore now be withdrawn.

In view of the present remarks it is believed that claims 1, 2, 4, 7, 8, 27-29, 31, 41 and 42 are now in condition for allowance. Reconsideration of said claims by the

Examiner is respectfully requested and the allowance thereof is courteously solicited.

CONDITIONAL PETITION FOR EXTENSION OF TIME

If any extension of time for this response is required, Applicants request that this be considered a petition therefor. Please charge the required petition fee to Deposit Account No. 14-1263.

ADDITIONAL FEE

Please charge any insufficiency of fee or credit any excess to Deposit Account No. 14-1263.

Respectfully submitted,
NORRIS, McLAUGHLIN & MARCUS, PA

By /William C. Gerstenzang/
William C. Gerstenzang
Reg. No. 27,552

WCG/tmo
875 Third Avenue - 8th Floor
New York, New York 10022
(212) 808-0700